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13. ABSTRACT *(Maximum 200 words)*

This is a follow-up study of a cohort of African-American and Caucasian women who were diagnosed with breast cancer in the late 1980's. Its purpose is to examine race differences (black/white) in breast cancer survival. In addition to measuring survival and examining racial differences in survival, this study also seeks to identify prognostic factors related to survival for the study population and to determine if the prognostic indicators are the same for women of both races.

At the end of year three of this four-year project, our preliminary results indicate a survival disadvantage for black women compared with white women with breast cancer, before and after adjustment for stage at diagnosis. Early findings suggest that the survival differential is not explained by race differences in socioeconomic status as measured with years of education. Over the course of the study, these findings will be expanded using more complete data on vital status, cause of death, and time to recurrence. Additionally, we will evaluate the prognostic significance of a wide range of factors including medical care and psychosocial variables, other tumor characteristics, and molecular alterations, thus permitting a multidisciplinary approach to understanding the black/white survival difference in breast cancer.

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John A Dhes 7/20/99

PI - Signature Date

TABLE OF CONTENTS

STANDARD FORM 298.....2

FOREWARD.....3

INTRODUCTION.....5

PROGRESS WITH RESPECT TO STATEMENT OF WORK.....5-7

GOALS FOR UPCOMING YEAR.....8

KEY RESEARCH ACCOMPLISHMENTS.....8

UPDATED PRELIMINARY FINDINGS.....8

REPORTABLE OUTCOMES.....9

CONCLUSIONS.....9

APPENDIX (ABSTRACT-PRELIMINARY FINDINGS).....10-11

INTRODUCTION

This is a follow-up study of a cohort of African American and white women who were diagnosed with breast cancer in the late 1980s. The study aims are to examine race differences in survival, examine predictors of survival for all study subjects (controlling for race), and to identify race-specific predictors of survival. The primary objective is to identify factors that explain the observed race difference (African American/white) in survival from breast cancer. Factors to be evaluated include demographic variables, socioeconomic status, psychosocial factors, comorbidity, breast cancer treatment modalities, tumor characteristics, and specific genetic alterations.

PROGRESS TO DATE WITH RESPECT TO ORIGINAL STATEMENT OF WORK

Task 1: Month 1-1.5: Hire project coordinator/ **COMPLETED**

UPDATE:
Early in year 03, Ms. Gwatkin left this position for another position outside the University. Ms. Lisa Schlenk assumed her duties on a part-time basis. Ms. Schlenk has worked with the PI on another investigation since 1996. The transition went smoothly as Ms. Schlenk had been working in an adjoining office since the beginning of this study, and was well-acquainted with the daily routines associated with this position. In addition, she brought to the position sophistocated computer skills that were helpful in data management

Task 2: Months 1-6: Submit protocol to 22 hospitals to gain approval from the Institutional Review Boards. This requires a significant amount of paperwork as well as personal appearances by the P.I. and the RCA director. **COMPLETED**

Task 3: Months 1-12: Develop and learn a data tracking system. This will be preceded by the purchasing of a new computer and appropriate software. **COMPLETED**

Task 4: Months 1-3: Review all existing files on patients to establish a comprehensive list of hospitals in which tumor specimens might be located. This is not a task that can be computerized, because the existing data is part of original documentation that was abstracted from patients' medical charts. **COMPLETED**

Task 5: Months 7-9: Collect tumor specimens from 22 hospitals. **COMPLETED**

UPDATE:
It is assumed that we have collected all specimens that will be available to us. Nevertheless, we are still pursuing the retrieval of tissue from 3 hospitals: St. Raphaels (17 cases) , Uconn (3 cases) and Greenwich Hospital (3 cases). While the specifics differ, in all 3 of these hospitals, our study and a number of other research projects have been denied access to tumor blocks to date. Our representative from the RCA (Shared Resource from the Yale Cancer Center) makes weekly inquires as to the availability of the requested blocks. In the case of St Raphael's Hospital, we have offered to hire our own histology technician to make the necessary sections. To date, our offer has not been accepted. We will continue to make the requests through December, 1999. If, by then, we still have not received the tumor tissue, we will assume that these cases will have missing data.

Task 6: Months 7-9: Link study cases to Connecticut Tumor Registry files. **COMPLETED IN 1997; DATA INCLUDED IN PRELIMINARY RESULTS PRESENTED AT ERA OF HOPE MEETING**

UPDATE:
All CTR data were updated in the early months of 1999. The PI (Dr. Jones) and a part-time research assistant, Dr. Kent Ta made several trips to the Connecticut Tumor Registry in Hartford in order to read the on-line file on every study subject. Any new information was abstracted.The CTR no longer provides this information by computer tape, thus, this was a labor intensive task that required several trips to the registry. We also used hard copies of information provided by Connecticut hospitals to resolve issues of missing or ambiguous information. This updated information on vital status, time to recurrence, and treatment modalities has been incorporated into our data base.

Task 7: Months 9-12: Select from all available paraffin blocks on each patient, the best specimen (tumor block) for further testing. This will require a review of tumor slides (and preliminary staining) by the pathologist. **COMPLETED (with the exception of specimens from the hospitals named above)**

Task 8: Months 13-24: Laboratory testing on approximately 300 tissue samples. Tests to be done are the following: Histopathologic grade, tumor grade, estrogen receptors, progesterone receptors, DNA ploidy, S phase fraction, presence of p53 mutations, and overexpression of erbB-2. Additionally, gene sequencing will be done on all tumors that are positive for p53 in order to determine location and type of mutation. . **COMPLETED (with the exception of specimens from the hospitals named above)**

UPDATE:
Laboratory testing has been completed on specimens from 254 study subjects. Although we projected receiving tumor on 300 patients, we were unable to retrieve specimens from 3 institutions (discussed above). Additionally, a number of tumor blocks either had no or insufficient tumor to perform the tests discussed in the protocol. All available blocks were tested for tissue. Several changes to the original protocol were made: 1) Histopathologic grade will be evaluated from the original pathology reports; 2) DNA ploidy was performed on approximately 80 specimens. At that point, under the advice of Drs. Howe and Lachman, the PI decided that this was consuming too much tissue and was unlikely to yield results that have not been previously reported. Instead, we decided to add a new test: c-met, as described in the 1998 annual report. Additionally, a Yale Cancer Center colleague (and fellow DOD grant recipient), Dr. Michael DiGiovanna, has reported interesting findings on the activated form of neu, p-neu. (Phospho-neu) After receiving Yale HIC approval, we submitted tumor tissue to his laboratory for p-neu testing. These tests will be completed in the next several weeks. Although these changes represent slight departures from the original protocol, the decision was made to explore the newest avenues of research on prognostic indicators.

Task 9: Months 13-30: Review all original documentation (e.g., progress notes, M.D.consults, discharge summaries), patient interviews for available data on treatment for cancer. Compare these data with CTR data. Fill in the blanks: i.e., contact physicians, specialists, or patients in order to gain as complete information as is possible. **COMPLETED**

Task 10: Months 13-30: This task will be coordinated with task 8, in that a similar review of all available data will be conducted to ascertain vital status (including recurrence or development of subsequent primary cancer). **COMPLETED**

UPDATE, TASKS 9 AND 10: All data have now been collected and are included in study data bases. Once the data were collected , Dr.Ta (M.D.) reviewed all information to identify deficiencies in the information and to resolve inconsistencies in the data from different data sources.

Task 11: Months 12-18: Data Management. Even though the data will be "trickling" in over the next year and one-half, the development of SAS datasets will be underway well in advance of having completed data collection. This will involve the assimilation of several different data sources with existing data to develop SAS data sets, as well as creation of variables, and various indices (especially relevant to the psychosocial variables). **COMPLETED**

UPDATE: As mentioned above, Dr. Kent Ta joined the study in December, 1998 as a research assistant and data manager. He was instrumental in establishing our 5 complete data bases: a) In-person Interview data; b) Medical record abstraction data; c) Tumor registry data; d) MD questionnaire data; e) Laboratory data; These data sets have been cleaned with variables identified and transformed into SAS data sets.

Task 12: Months 18-end of project period: Data Analysis. The timing of this task will depend on the availability of the data. Because of the scope of the proposed project, and the availability of existing data, it is reasonable to plan for data analyses even before all data are available.

UPDATE:
As the new data sets have only recently become available, we have performed only basic analyses since the earlier analyses that were presented at the 1997 Era of Hope meeting. These new results are appear below, See UPDATED PRELIMINARY FINDINGS.

Task 13: Year 04: Write-up of results. Clearly, the reporting of results needs to be done in conjunction with on-going analyses. Other than preliminary reports, we anticipate that the major write up will take place in the last year of the study.

UPDATE:
To be performed in Year 04 as planned.

Goals for the Upcoming Year

To begin, with the exception of major data analysis, all of the tasks outlined in last year's "Goals for the Upcoming Year" were accomplished. The primary activities to be accomplished in year 04 are data analysis and manuscript preparation. Additionally, there are some final lab tests to be performed (on the specimens from the 3 hospitals that have not yet provided tumor tissue), as well as final reading of the p-neu results and SSCP, DNA sequencing by the study pathologist. Additionally, there is a fairly large administrative task to be performed in that all tumor blocks and slides must be returned to the 22 participating community hospitals. Because we received many blocks and slides on each patient, and much of this material is still in the hands of several different laboratories, this task and continuing data management will be one of several tasks assigned to the project coordinator.

KEY RESEARCH ACCOMPLISHMENTS

Preliminary Findings: NOT for PUBLICATION

- Established race difference in survival from breast cancer, after adjustment for stage at diagnosis

- Established race differences for a number of prognostic indicators, confirming earlier reports of a disadvantage for African American women compared to white women

- Earlier results suggest that survival differences persist even with adjustment for socioeconomic status (measured as Education)

Once analyses are completed using the updated survival information, treatment information, and time to recurrence, more definitive and comprehensive findings will be reported.

UPDATE OF PRELIMINARY FINDINGS

Since reporting preliminary results in 1997, we now have a minimum of 10 years of follow-up on the original cohort of 322 breast cancer study subjects. Of these, 135 (42%) women have died. Eighty-four (26%) deaths are directly attributable to breast cancer. Disease-free survival (alive, without recurrence) in this cohort is 54% (175 women).

Early analysis of the laboratory data shows that African American women are significantly more likely to be diagnosed with estrogen receptor negative tumors (Odds ratio [OR] = 1.82 , Confidence Interval [CI] 1.04 – 3.20) and to be positive for p53 mutations (OR = 3.71, CI 1.54 – 9.12), both of which are associated with poor prognosis. African American women were also more likely to be diagnosed with progesterone receptor negative tumors (OR = 1.23, CI 0.68 – 2.22) and tumors which were positive for c-met (OR = 1.21, CI = 0.69 – 2.13), although neither of these differences approached statistical significance. In this cohort of breast cancer patients, African American women were not more likely to be diagnosed with tumors which overexpressed neu (OR

0.85, CI 0.46 – 1.60). This is consistent with the only 2 known studies to report on race differences in neu.

REPORTABLE OUTCOMES:

Beth A. Jones, Ph.D., Meredith S. Glazer, Ph.D., Stanislav V. Kasl, Ph.D.
Yale University School of Medicine
RACE DIFFERENCES (BLACK/WHITE)
IN BREAST CANCER SURVIVAL. EARLY FINDINGS.
Abstract presented at the 1997 Era of Hope meeting in Washington,DC.

To date, there have been no other published or publicly presented abstracts from this investigation.

CONCLUSIONS:

At the end of year 03 of this four-year epidemiologic study, preliminary results indicate a survival disadvantage for African American women compared with white women with breast cancer, before and after adjustment for stage at diagnosis. Early findings indicate that the survival disadvantage is not explained by race differences in socioeconomic status as measured by years of education. At this juncture, all of the necessary data have been assembled. In this last year of the study, in-depth analyses will be undertaken to determine the prognostic significance of a wide range of factors including medical care, comorbidity, treatment modalities, psychosocial factors, tumor characteristics, and molecular alterations. Outcomes include overall survival and disease free survival over a 10 year (average) follow-up period. This study offers a multidisciplinary approach to understanding the African American /white survival difference in breast cancer.

APPENDIX: Abstracts presented at the 1997 Era of Hope meeting in Washington, D.C.

RACE DIFFERENCES (BLACK/WHITE) IN BREAST CANCER SURVIVAL. EARLY FINDINGS.

Beth A. Jones, Ph.D.,
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Despite a somewhat lower incidence of breast cancer in African American women relative to white women, there is a substantial black/white difference in survival from breast cancer. Data from the Surveillance, Epidemiology , and End Results (SEER) program for the years 1986-1992 indicate a five-year survival rate of 85% for white women compared with 70% for black women. While the survival rates for women of both races have improved significantly since the mid 1970s, the survival rates reported for black women in this latest time period are comparable to the survival rates achieved for white women nearly twenty years ago.[1] The purpose of the current investigation is to evaluate the survival in a cohort of black and white women who were diagnosed with breast cancer in Connecticut between 1987 and 1989, and to identify important prognostic factors, with special emphasis on explaining the black/white survival differential.

This follow-up study builds on the results of a completed, population-based investigation aimed at understanding social, psychological, and medical care factors that might explain the observed black/ white difference in stage at diagnosis of breast cancer. Previously collected data (from the time of diagnosis) will be combined with newly collected data on molecular alterations (p53 and erbB-2) and tumor characteristics (e.g., DNA ploidy, estrogen receptor status) derived from laboratory testing of archived tissue blocks, as well as vital status information retrieved from the Connecticut Tumor Registry (CTR) to determine the following: 1) predictors of survival from breast cancer for all study subjects; 2) race-specific predictors of survival; and 3) the explanatory potential of prognostic variables in the black/white survival differential.

Keywords: Race, Survival, Blacks, Prognostic Factors, Breast Cancer

This work was supported by the U.S. Army Medical Research and Materiel Command under DAMD-17-96-1-6101

Lay Abstract

This is a population based study of 145 black women and 177 white women who were diagnosed with breast cancer in Connecticut between January, 1987 and May, 1989. Women were identified through active surveillance of 22 Connecticut hospitals. Extensive baseline information was collected from in-person interview and medical chart abstraction. In this first year of the follow-up study, information on vital status and cause of death has been obtained from the CTR. Preliminary data analysis includes bivariate analyses of race and potential prognostic factors using chi-square tests; predictors of survival have been evaluated with Kaplan-Meier product limit estimates and Cox proportional hazards models. In these preliminary analyses, all cause mortality is the outcome variable.

As of January, 1997, 113 women of the 322 breast cancer cases (35.1%) had died, with an average time to death of 4.2 years. Eighty-two (72%) of the deaths were confirmed breast cancer deaths. Among survivors, women were followed for a maximum of 9.6 years with an average follow-up of 7.2 years. Black women were significantly more likely to die than were white women during the follow-up period (age-adjusted Risk Ratio [RR] = 1.70, Confidence Interval [CI],1.16-2.50). Although adjustment for stage at diagnosis (*in situ*/ local vs. regional/remote) reduced the predictive value of race, black women were still significantly more likely to die from their disease than were their white counterparts (RR = 1.52, CI 1.03-2.24). Further adjustment of this model for one measure of socioeconomic status (years of education) did not alter these results.

Several tumor characteristics differed by race group, with black women more likely to be in the higher risk category. Using data abstracted from the medical chart, and adjusting for age, black women were more likely to have high grade tumors (Odds Ratio [OR] = 2.53, CI 1.08-5.91), lymphatic invasion (OR = 1.91, CI 0.99-3.69), necrosis (OR=1.48, CI 0.87-2.53), skin involvement 1.88 (0.66-5.36), nipple involvement (OR = 1.95, CI 0.77-4.99), estrogen receptor (ER) negative tumors (OR = 1.29, CI 0.70-2.39), and progesterone receptor (PR) negative tumors (OR= 1.50, CI 0.81-2.78). While several of these factors do not differ significantly between race groups, they suggest a tendency toward more aggressive tumors in black women. The lack of statistical significance may be a function of missing data as not all laboratory tests were performed on all tumors. Of the tumor characteristics listed above,
only skin involvement remained a significant predictor of mortality after adjustment for age, race, and stage at diagnosis.

These preliminary results demonstrate a survival disadvantage for black women compared with white women with breast cancer, before and after adjustment for stage at diagnosis. Early findings suggest that the survival differential is not explained by race differences in socioeconomic status as measured with years of education. Over the course of the study, these findings will be expanded using more complete data on vital status, cause of death, and time to recurrence. Additionally, we will evaluate the prognostic significance of a wide range of factors including medical care and psychosocial varibles, other tumor characteristics, and molecular alterations, thus permitting a multidisciplinary approach to understanding the black/white survival difference in breast cancer.

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